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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

MOORE, WILLIAM W

ART UNIT	PAPER NUMBER
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1656

DATE MAILED: 03/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/500,936

Applicant(s)

POULOSE, AYROOKARAN J.

Examiner

William W. Moore

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 December 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-18 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-18 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Priority

Applicant's claim in the Declaration of Inventorship to priority under 35 U.S.C. § 119 of the 16 January 2002 filing date of the parent US provisional application serial No. 60/350,222, and its successor International patent application PCT/US03/01448 filed 16 January 2003, of which the instant application is a National Stage filing under 35 U.S.C. § 371, is hereby acknowledged.

Information Disclosure Statement

No Information Disclosure Statement [IDS] has yet been filed in this application.

Election and Preliminary Amendment

Applicant's election without traverse in the Response filed 23 December 2005 of the invention of Group III, comprising subtilisin variants having an amino acid substitution at a position corresponding to position 26 in the subtilisin BPN amino acid sequence set forth in SEQ ID NO:2, is acknowledged. Applicant's Preliminary Amendment filed on 23 December 2005, has been entered, amending claims 1, 4, 7 and 13. Applicant also indicates that claim 10 is an amended claim but no amendment is apparent. Claims 1-18 herein are examined to the extent that they describe subtilisin variants comprising an amino acid substitution at the subtilisin BPN'-correspondent position 26, polynucleotides that encode such variants, and cleaning compositions comprising such variants.

Objections to the Specification

The specification is objected to for reciting, at page 1, the undefined term "carbonyl hydrolases" because it fails to indicate any particular group of polypeptides or enzymes that have a structure within which a structure of a serine protease might be recognized.

The specification is further objected to for omission of the provisional application serial No. 60/440,792 at line 24 of page 17.

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Compliance with 37 CFR § 1.821 is required in response to this Office action. (1) Page 2, line 7, lacks a designation describing the recited amino acid positions according to requirements of 37 CFR § 1.821 for a Sequence Disclosure which call for a statement in the form of the designation "**SEQ ID NO:n**", where "n" is an integer corresponding to the Sequence Disclosure, whether a sequence is referred to in whole or in part. At page 2, the several positions are indicated without reference to a particular sequence, where the amino acid sequence of SEQ ID NO:2 is intended. (2) In addition, page 21 lacks the necessary designations, at lines 14 and 16, for the nucleotide sequences of the disclosed forward and reverse primers. (3) While Applicant's PCT priority document provides a Sequence Listing, there is no printed sequence listing present in the file of the instant application. Each of these three defects must be corrected in response to this communication and a Statement of Sameness of the printed and computer-readable forms of the sequence listing must also be submitted. It is noted that there is no disclosure of the amino acid sequence of the GG36 subtilisin. Please also note that if the nucleotide sequences of the primers disclosed at page 21 were **not** provided in the computer readable form [CRF] of the sequence listing submitted in the priority document, or if Applicant desires that the amino acid sequence of GG36 subtilisin be disclosed in the specification, such further oligonucleotide and amino acid sequences **MUST** be included in both (a) a revised/amended printed form of the sequence listing and (b) a revised computer readable form [CRF] that must both be submitted in response to this communication, again with an accompanying Statement of Sameness. See 37 CFR §§ 1.821(b), (c) and (d).

Claim Objections

Claims 1, 5, and 14 are objected to for the following informalities: Claim 1 is objected to because it mistakenly recites, "at one or more residue positions . . .

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selected from the group consisting of", yet the claim amendment results in the recitation of a single position in the claim. Appropriate correction is required, e.g., amending claim 1 to recite "having a substitution at the a position corresponding to position 26 in the subtilisin amino acid sequence set forth in SEQ ID NO:2."

Claim 5 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form. Claim 5 cannot further limit substitutions at the secondary substitution sites described by claim 4 from which it depends where claim 5 adds many more positions, i.e., positions 26, 47, 55, 66, 82, 92, 105, 113, 151 and 201.

Claim 14 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form. Claim 14 cannot further limit the substitutions at the secondary sites for substitutions described by claim 13 from which it depends where claim 14 adds an additional position, i.e., position 216.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4-8 and 10-14 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification fails to exemplify or describe preparation of protease variants that comprise a substitution at the elected subtilisin BPN'-correspondent position 26 and that

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meet functional limitations of claims 4-8 and 10-14. The specification is considered to provide an adequate written description of the subject matters of claims 1-3, 9, and 15-18 because claim 9 requires no more than the elected substitution of claim 1 and recites conditions that approximate those stated at pages 33 and 34 of the specification in Example 7. This example teaches how to determine whether or not a disclosed variant has an improved thermal stability by comparison with a native GG36 subtilisin that has a 269 amino acid sequence closely related to that of the prior art subtilisin 309, which has the amino acid sequence set forth in SEQ ID NO:6 herein, and also related to the similar amino acid sequences of the prior art subtilisins 147 and PB92.

The rejected claims 4-8 and 10-14, however, describe generic subtilisin variants - in claims 6 and 12 - as well as specific subtilisin variants - in the ambiguously stated claims 4 and 5 and in the more clearly stated claims 7, 8, 10, 11, 13 and 14 - that are not disclosed to have improved thermal stability, as recited in claim 2 and required by claim 3, and that the temperature conditions stated in claim 9 inherently require. Apart from the ambiguous recitation of 26S and 26T substitutions as secondary substitutions in claim 4, only the generic claims 1-3 and 9 describe an elected subtilisin variant that has an improved property, relative to a native GG36 subtilisin, that is supported by the disclosure of the specification: improved thermal stability. See the specification's Table 4 at page 34 for V26T substitution and at page 36 for the paired V26S+N218S substitution. It is noted that no pending claim now identifies the prior art substitution N218S, known to enhance thermal stability in subtilisins generally, as a secondary substitution. The specification does not otherwise disclose or teach that a subtilisin variant that does not comprise an amino acid substitution including the elected subtilisin at the BPN'-correspondent position 26 has any kind of improved characteristic other than improved thermal stability. The specification particularly fails to disclose or teach

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that any positions recited in claims 4, 7, 8, 10, 11, 13 or 14 can be combined with a substitution at the elected position 26 to improve thermal stability. "While one does not need to have carried out one's invention before filing a patent application, one does need to be able to describe that invention with particularity" to satisfy the description requirement of the first paragraph of 35 U.S.C. § 112. *Fiers v. Revel v. Sugano*, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993). The specification provides no relevant identifying characteristics of protease variants having improved wash performance in conditions of, e.g., claims 6 and 12, wherein amino acid sequence alterations other than a substitution at the subtilisin BPN'-correspondent position 218 are combined with a substitution at the subtilisin BPN'-correspondent position 26, whether in the recited reference sequence of subtilisin BPN' set forth in SEQ ID NO:2, or in a subtilisin having a sequence more closely-related to Applicant's exemplified GG36 subtilisin amino acid sequence such as the subtilisin 309 sequence set forth in SEQ ID NO:6.

Claims 4-8 and 10-14 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for improving the thermal stability of members of the class of serine proteases known as subtilisins, or subtilases, by comparison with the unmodified amino acid sequence of a GG36 subtilisin by introducing an amino acid substitution at a position identified by correspondence with position 26 in the sequence set forth in SEQ ID NO:2, does not reasonably provide enablement for modification of members of other classes serine proteases or proteases generally to provide an improved wash performance by comparison with the unmodified amino acid sequence of a GG36 subtilisin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 4-8 and 10-14 contemplate additional amino acid substitutions in any kind of protease at positions other than the elected subtilisin BPN'-correspondent position 26 that might provide an improved thermal stability or, as in claim 2, an improved wash performance. Yet the specification discloses no improved wash performance in any protease, and no improved thermal stability in proteases generally, save for improved thermal stability in a subtilisin due to a substitution at the subtilisin BPN'-correspondent

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position 26 in one particular subtilisin, a GG36 subtilisin, the amino acid sequence of which is not closely related to the amino acid sequence of the subtilisin BPN' that claim 1 recites as the reference sequence for modifications. It is noted that the specification provides no disclosure of the amino acid sequence of the GG36 subtilisin, yet valine is disclosed to reside at position 26 in the amino acid sequences of the mature GG36 subtilisin, the mature subtilisin 309, and the mature subtilisin BPN'. Consequently, the specification is considered to support modification of subtilisin amino acid sequences generally to produce an enhanced thermal stability by the amino acid substitutions V26S and V26T at the subtilisin BPN'-correspondent position 26. The specification, however, is not considered to support improved thermal stability in subtilisins generally by further amino acid substitutions at amino acid sequence positions recited in claims 4, 5, 7, 8, 10, 11, 13 or 14, or to support any other kind of improved wash performance in subtilisins generally by the introduction of an amino acid substitution at the position corresponding to position 26 in the amino acid sequence of SEQ ID NO:2. This is because the specification teaches the nature of such improvements only by reference to particular conditions and only by the modification of a particular subtilisin amino acid sequence, that of the subtilisin GG36, and because the addition of further amino acid substitutions in other subtilisin amino acid sequences at positions not taught to be compatible with the particular substitutions at position 26 in the GG36 subtilisin that improve thermal stability cannot be considered to provide a similar improvement where a combination with such further positions is just as likely to reduce thermal stability. It is noted that the compatible, further, substitution N218S disclosed in Tables 1 and 4 is not recited or otherwise provided for in any pending claim. Mere sequence perturbation cannot enable the design and preparation of divergent proteases that provide the public with an improved characteristic required by claims 4, 5, 7, 8, 10, 11, 13 or 14.

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It is well settled that 35 U.S.C. § 112, first paragraph, requires that a disclosure be sufficiently enabling to allow one of skill in the art to practice the invention as claimed without undue experimentation and that unpredictability in an attempt to practice a claimed invention is a significant factor supporting a rejection under 35 U.S.C. §112, first paragraph, for non-enablement. See, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (discussing eight factors relevant to analysis of enablement). Applying the factors discussed in *Wands* to Applicant's disclosure, it is apparent that:

- a) the specification lacks adequate, specific, guidance for altering serine protease amino acid sequences structurally unrelated to the amino acid sequence set forth in SEQ ID NO:2 in order to provide an improved characteristic required by the claims,
- b) the specification lacks working examples wherein protease amino acid sequences unrelated to the sequence set forth in SEQ ID NO:2, are altered to provide any of the improved characteristics required by the claims,
- c) in view of the prior art publications of record herein, the state of the art and level of skill in the art do not support such alteration, and,
- d) unpredictability exists in the art where no members of other classes of serine proteases having amino acid sequences unrelated the amino acid sequence of the mature subtilisin BPN' set forth in SEQ ID NO:2 have had more than a few amino acids identified for concurrent modification, and to no particular effect.

Thus the teachings of the specification and the prior art cannot be combined to support the scope of the divergent proteases embraced by claims 4-8 and 10-14.

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-18 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rejected as indefinite because there can only be a single amino acid position in the amino acid sequence of a "protease" that is "equivalent" to position 26 in the reference *Bacillus amyloliquefaciens* subtilisin amino acid sequence set forth in SEQ ID NO:2. If "one or more . . . residue positions" were identified as "equivalent", then the artisan and the public would not be able to determine the metes and bounds of

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the intended subject matter. Claims 2-18 are included in this rejection because they depend from claim 1 but fail to resolve its ambiguity. In particular, the recitation of claim 6 increases the ambiguity of claim 1 from which it depends.

Claim 2 is independently rejected as indefinite because it fails to recite two distinct properties from which an improved property can be selected where a generic, improved, stability is indistinguishable from an improved wash performance, particularly where the claim describes no parameters with which the artisan or the public seeking to determine the metes and bounds of the intended subject matter can recognize an improvement.

Claim 6 is independently rejected as indefinite for two reasons: (1) it depends from claim 4 which recites "further comprises" thus must comprise a substitution at a different position than that recited in claim 1, but then ambiguously includes two substitutions at the same position recited in claim 1, and (2) it recites substitutions at positions not stated in claim 4 or any other preceding claim even though it depends from claim 4, thus the artisan and the public would not be able to determine the metes and bounds of the intended subject matter. Claims 11 and 14 are likewise independently rejected as indefinite because both recite more positions for substitution than claims 10 and 13 from which they respectively depend. Amending claims 6, 11 and 14 to remove the position of claim 1 where a substitution is already required and to remove substitutions at the positions not stated in claims 4, 10 and 13 will overcome this aspect of the rejection, and the excess positions may be presented in separate claims.

Alternatively, amending claim 6 to remove the position of claim 1 where substitution is already required and amending claims 4, 10 and 13 to provide recitations supporting the other substitutions stated in claims 6, 11 and 14, to the extent such amendment is supported by the disclosure of the specification, will overcome this aspect of the rejection.

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Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1 and 15-17 are rejected under 35 U.S.C. § 102(b) as being anticipated by Pantoliano et al., US 4,908,773, who disclose the preparation of DNA sequence encoding a variant subtilisin BPN' having an amino acid substitution at position 26, an expression vector comprising the variant-encoding DNA sequence, and a host cell transformed with the vector, as well as the recombinant production by the host cell of a proteolytically active subtilisin BPN' comprising an amino acid substitution at position 26, specifically the substitution V26C, meeting the limitations of claims 1 and 15-17 herein. See, e.g., Tables 2 and 5 and columns 23-31. Pantoliano et al. disclose that the V26C-substituted subtilisin BPN' was "approximately as stable as the wild-type protein", i.e., the native, mature, subtilisin BPN'. See col. 30 at lines 20-22.

Claims 1 and 15-18 are rejected under 35 U.S.C. § 102(e) as being anticipated by Rubingh et al., US 6,946,128, who disclose the preparation of DNA sequence encoding a variant subtilisin BPN' having an amino acid substitution at position 26, an expression vector comprising the variant-encoding DNA sequence, and a host cell transformed with the vector, as well as the recombinant production by the host cell of a proteolytically active subtilisin BPN' comprising an amino acid substitution of cysteine or lysine at position 26, that permits the masking of an exposed epitope region, meeting the limitations of claims 1 and 15-17 herein. See, e.g., col. 3 at lines 56-59, col. 6 at lines

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30-34, cols. 7 and 10-13, and claims 1 and 10. Rubingh et al. further disclose cleaning compositions, such as detergent compositions, comprising a subtilisin having an amino acid substitution at the subtilisin BPN'-correspondent position 26, meeting the limitations of claim 18. See cols. 18-24 and claim 19.

Allowable Subject Matter

Not subject to the rejections above over the prior art because the substitutions at position 26 the specification discloses to confer improved thermal stability 26, V26T and V26S, are neither disclosed nor suggested by the prior art of record herein, claims 2, 3, and 9 would be allowable if claim 1 were amended to describe a substitution of either V26T or V26S at a positions corresponding to position 26 in the amino acid sequence of SEQ ID NO:2. Canceling claims reciting substitutions at subtilisin BPN'-correspondent positions other than the compatible N218S substitution, and presenting a claim that specifies a further, N218S, substitution, is suggested.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 571.272.0933 and whose FAX number is 571.273.0933. The examiner can normally be reached Monday through Friday between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisory Primary Examiner, Dr. Kathleen Kerr, can be reached at 571.272.0931. The official FAX number for all communications for the organization where this application or proceeding is assigned is 571.273.8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571.272.1600.

William W. Moore
16 March 2006


KATHLEEN M. KERR, PH.D.
SUPERVISORY PATENT EXAMINER